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(54) Title: COSMETIC, SKIN-RENEWAL STIMULATING COMPOSITION WITH LONG-TERM IRRITATION CONTROL		
(57) Abstract A cosmetic skin-renewal stimulating composition suitable for daily use by consumers and providing anti-aging benefits with control of delayed irritation. The invention adds small quantities of a naturally occurring small-molecule, biologically active, aliphatic aminodiol lipid, for example sphingosine, to cosmetics incorporating a skin-renewal stimulating acid, for example lactic, hydroxybenzoic or retinoic acid, to provide control of deferred hyperproliferative allergenicity induced by the skin-renewal stimulating acid. Comparative data show a beneficial control of long-term irritation induced by several weeks of daily use of a variety of skin-renewal stimulating acids. The novel activity is displayed by sphingosine alone among several classes of biologically active skin lipids, in a selective and surprising manner. The results suggest applicability of the invention to wider classes of cell-proliferation agents for the control of deferred hyperproliferative allergenicity.		

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**COSMETIC, SKIN-RENEWAL-STIMULATING COMPOSITION
WITH LONG-TERM IRRITATION CONTROL**

TECHNICAL FIELD

5 This invention relates to a novel skin-renewal
stimulating composition and its method of application or
use. More particularly, it relates to a cosmetic
composition, especially a cosmetic composition suitable
for daily use, which can improve the appearance and
10 condition of the skin by stimulating, or increasing the
rate of, cell renewal. Some such compositions are known
as exfoliants and, more potent exfoliants are known as
skin peels. Skin peels are usually applied under
professional supervision. Often one application,
15 accompanied by suitable preparatory treatments such as
degreasing and abrasion, is adequate to induce peeling
and promote the growth of a "new" skin.

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BACKGROUND

It is well known, and the subject of ordinary biology text books, that the skin is a complex system with protective epidermal layers, growing endodermal layers, often a keratinous outer layer, systems of glands and follicles and systems for the supply of intracellular and extracellular fluids. Active methods and compositions for treating the skin which do more than provide a passive coating on it, must take account of its complexity.

15

Skin renewal can be stimulated, as a natural process, by removal of the outer keratinous layer of the skin system. Such removal can be effected mechanically, for example, abrasively by rubs, brushing and even scraping, or shaving. Chemical exfoliation and peeling are effected by agents that interact with the complex structure of the skin.

Known skin-renewal stimulating compositions and agents can provide anti-aging benefits, for example, a reduction of effects such as keratoses, freckles, wrinkles, elastosis and epidermal and dermal atrophy.

Recent years have seen the widespread use, by consumers and professionals alike, of a range of cosmetic and pharmacological formulations providing anti-aging and dermatologically therapeutic benefits. Active ingredients of these formulations typically include an alpha hydroxy acid ("AHA's" in the popular literature) or a retinoic acid (marketed under the names RETIN A or RENOVA, trademarks of Ortho Pharmaceuticals). Some currently available commercial formulations are described in "Mirabella", January 1993, pages 60-61.

Reputable scientific and clinical reports, as well as much subjective evidence have shown that substantial

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5 improvements in skin appearance and condition can be
obtained by means of skin-renewal stimulating acids. In
general terms, these improvements are believed to be
attributable to increased rates of skin cell renewal, and
the removal of outer layers of dead cells.

10

It is also well known that skin-renewal stimulating acids
can be irritating, and that the irritation they induce is
often a long-term effect manifested several weeks after
use of the acids. In extreme cases the irritation can be
15 severe, damaging and painful.

Hermitte et al. "Aged Skin, Retinoids and Alpha Hydroxy
Acids" Cosmetics and Toiletries 107 pp. 63-67 (July 1992)
provides a short review of the title subject, with a
20 substantial bibliography of forty references. The
disclosures of Hermitte et al. and the references listed
therein are herein incorporated by reference thereto.
Such disclosure includes details of many skin-renewal
stimulating acids that can be used in the practice of the
25 present invention.

SUMMARY OF THE INVENTION

The invention, as claimed, is intended to provide a
30 remedy. It solves the problem of reducing long-term
irritation induced by topical application of skin-renewal
stimulating acids to the skin. The invention solves this
problem by formulating the acids, either as a cosmetic or
a medication, with a small quantity of a sphingosine
35 material. Sphingosine is one of a vast number of
naturally occurring lipids or fatty substances that is
present in the skin of mammals and is believed safe as
well as effective and substantially free of side effects.

40 Clinical studies we have conducted have shown a
surprising and selective activity of sphingosine in

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5 controlling long-term irritation produced by repeated
applications of small dosages of skin-renewal stimulating
acids. Our test results show that, other classes of skin
lipids, namely phospholipids, cerobrosides and ceramides,
show little if any activity, in controlling long-term
10 irritation. Of the materials tested, sphingosine alone
displayed a clear reduction of a pronounced irritation
that was induced in volunteers by four weeks of treatment
with topically applied doses of skin cell-renewal
stimulating acids, namely, alpha hydroxy acids and
15 tretinoin, an isomer of retinoic acid. Ceramides, in
particular, which have recently been used in combination
with alpha hydroxy acids in moisturizing products, showed
no significant activity, in clinical studies, in reducing
either immediate or long-term irritation

20 Accordingly, the novel cosmetic and medicant compositions
of my invention are expected to provide new, consumer and
over-the-counter products that offer the effectiveness of
known skin-renewal stimulating acids without the
25 unpleasant, and sometimes damaging, long-term irritation
with which the use of these acids has heretofore been
associated.

Further data we have obtained indicates that the role of
30 an added sphingosine material in controlling long-term
irritation, induced by skin-renewal stimulating acids,
may be attributable to a more general role of replacing
deficiencies of sphingosine caused by cellular
immaturity. In keeping with these findings, the
35 invention also provides a cell-renewal stimulating
composition for topical application generally to
epithelial tissue. In this aspect of the invention,
enough sphingosine material to compensate for sphingosine
deficiencies attributable to cellular immaturity is
40 incorporated in a composition designed to stimulate
increased cell proliferation by incorporation of a

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- 5 suitable, known stimulatory agent, such as a drug or a hormone.

BEST MODE FOR CARRYING OUT THE INVENTION

- 10 In searching for a material to control long-term irritation, one avenue of inquiry is to investigate the substances that are found occurring naturally in the skin.

- Rieger "Skin Constituents as Cosmetic Ingredients"
15 Cosmetics and Toiletries 107 85-94 (November 1992) reviews the state of the art of skin constituents from the point of view of their suitability and efficacy as cosmetic ingredients. Of the myriad skin constituents, a large class is comprised by lipid, or hydrophobic, fatty
20 or fat-related materials. Described by Rieger as bewilderingly complex, (last two lines of the left-hand column of page 87), the composition of sebaceous lipids, one source of the lipid materials in the intercellular spaces of the epidermis, includes squalene, sterols, wax
25 and sterol esters and triglycerides. Another source of lipid materials is provided by production of sphingosine in basal keratinocytes, from which a wide class of sphingolipid materials is enzymatically synthesized. Acylation of sphingosine, phytosphinganine, or
30 derivatives of either, produces ceramides. Glycosation of ceramides yields cerebrosides. Ceramides and cerebrosides are additional classes of lipids found in the skin. In addition to sphingolipids and sebaceous lipids, other substances, like cholesterol, alkanes and
35 free fatty acids, are also present. Phospholipids are reported by Rieger as not being present in the stratum corneum, or outer layer of the skin though they are important lipid constituents of basal skin layers.
- 40 Jass et al. "The Living Stratum Corneum: Implications for Cosmetic Formulation", Cosmetics and Toiletries" 106 47-

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5 53 (October 1991), citing an earlier reference, report
concentrations of lipids found variously in the inner
basal and spinous layers of the epidermis, in the
granular layer and in the outer stratum corneum.
Sphingolipids are remarkable for showing an increase in
10 concentration, proceeding outwardly through these layers,
from about 7.3% of the (presumably intercellular) total
lipid content of the basal layer to about 24.4 % in the
stratum corneum where their presence is believed
important to the skin's barrier function and to
15 prevention of loss of water vapor. By the time they
reach the outer, stratum corneum, it appears from the
reported data that glycolipids (cerebrosides) are, like
phospholipids, substantially degraded, in this case to
ceramides. The fate of sphingosine, which is not
20 properly described as a sphingolipid, is not reported and
it is not clear whether Jass et al.'s studies included
sphingosine determinations.

In contrast to sphingolipids, phospholipids decline
25 dramatically from about 44.5% in the basal layers to
about 6.6% in the stratum corneum.

Clearly, no feasible research project could study all
skin constituents, or even all lipid constituents. The
30 field of study has to be narrowed down.

Rieger offers some principles for evaluating skin
constituents for cosmetic use, including guidelines as to
groups of substances not likely to be active in cosmetic
35 formulations. The stratum corneum, or outer layer of the
skin is not generally permeable to large molecules.
Accordingly, molecules over about 4-5,000 molecular
weight are contra-indicated for cosmetic uses that depend
upon permeation through the stratum corneum (last
40 complete paragraph, right-hand column page 86) for their
activity.

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- 5 Phospholipids are contra-indicated by the probability of hydrolytic attack and degradation, as they find their way through the epidermis to keratinocytes. With regard to sphingolipids, Rieger concluded that there is no evidence that cosmetically supplied components of ceramides, 10 (except for linoleic acid) can be properly incorporated in the stratum corneum (last paragraph, right-hand column of page 88). This conclusion does not suggest that ceramide components would be useful as active cosmetic ingredients. In contrast, Petersen in "Ceramides: Key 15 Components for Skin Protection", Cosmetics and Toiletries 107 pp. 45-49 (February 1992) concludes that, from a pharmaceutical and cosmetic point of view, ceramides are among the most important compounds for skin protection.
- 20 With regard to sphingosine, (a structural component of ceramides), Rieger notes that although sphingosine occupies a key role in the structure of many lipids, glycosphingolipids (cerebrosides), seem to exert structure-specific effects on the in vitro proliferation 25 rates of human keratinocytes. This would suggest that cerebrosides rather than sphingosine would be useful in stimulating skin cell renewal. Current literature reports known to applicants lack clear teachings as to the presence or function, if present, of sphingosine in 30 significant quantities in the stratum corneum.

Many in vitro, and small-mammal investigations of the mechanism of action of sphingosine have been conducted, from which sphingosine has become known as a protein 35 kinase inhibitor, leading to suggestions that it may be useful in the treatment of diseases, or clinical disorders, such as psoriasis. One such report is from Gupta et al. "Sphingosine Inhibits Phorbol Ester Induced Inflammation etc." J. Invest. Dermatol. 91:486-491, 1988. 40 The data relates to mouse skin so that any conclusions

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5 that may be drawn from it carry uncertainty as to whether they accurately model the behavior of human skin.

Neither Gupta et al., nor any other art, suggests that sphingosine can control long-term irritation induced by skin-renewal stimulating acids, or suggests that
10 sphingosine can improve the long-term performance of skin-renewal stimulating acids. Control of immediately induced contact irritation is not an appropriate indicator of an ability to control long-term irritation,
15 as the data reported herein will show. Long-term irritation is induced by a different mechanism from short-term.

In the light of the foregoing knowledge of the art, we
20 initiated clinical studies designed to evaluate, for their efficacy in controlling undesirable long-term side effects of skin-renewal stimulating acids, a practical range of skin lipid materials. For this purpose, we selected a limited number of groups of lipid substances,
25 namely sphingosine, ceramides, cerebrosides and a representative phospholipid, lecithin. This line of investigation was pursued in spite of the cost of some of these materials which presents a formidable barrier to their use in cosmetic preparations, for example, the cost
30 of one source of sphingosine is of the order of \$5,000.00 per kilogram, for a twenty percent material, and that of ceramides and cerebrosides is comparable.

As will be reported and explained hereinbelow, the data
35 we obtained showed sphingosine to have a surprising activity not shared by cerebrosides or ceramides, or by the tested phospholipid.

Broadly stated, the present invention provides a skin-
40 renewal-stimulating, cosmetic composition for frequent and repeated, or daily, topical application to normal

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5 skin. The composition has an acidic pH and comprises a
cosmetically acceptable, skin-cell-renewal stimulating
acid or acids, present at a sufficient concentration to
improve the appearance of the skin, together with a
proportion of a sphingosine material sufficient to
10 control long-term irritation.

Sphingosine material

The preferred sphingosine material for use in practicing
this invention is sphingosine itself, in a substantially
15 pure form, so far as availability permits. Sphingosine
is characterized under that name and monograph number
8703 in The Merck Index (Merck & Co. Inc.) eleventh
edition 1989. It is a chiral, amino diol with a
thirteen-carbon aliphatic chain, constituting a
20 hydrophobic tail. Preferably the naturally occurring
D(+)-erythro enantiomer is used. To this end,
sphingosine derived from biological sources, for example
bovine brain extracts, can be used, although currently
active research efforts suggest that synthetic
25 sphingosine enantiomers, or racemic mixtures, may soon
become available.

Those skilled in the art will be familiar with equivalent
compounds to sphingosine itself, that display comparable
30 activity to sphingosine, and can be used in practicing
the present invention. Such compounds include analogs,
homologs, enantiomers and derivatives not only of
sphingosine but also of phytosphinganine, and
dihydrosphingosine. Some such compounds, and their
35 syntheses, are described in US Patents Numbers 5,110,987
(Liotta et al.), 4,952,683 (Tschannen et al.) and
4,937,328 (Schmidt et al.), the disclosures of which are
herein incorporated by reference thereto.

40 Such sphingosine equivalents should, until a precise
mechanism of action of sphingosine in achieving the

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- 5 surprising results of the present invention is clearly known, apparently, preferably include the main chemical features of sphingosine, namely an electropositive nitrogen atom near one or two electronegative oxygen atoms, preferably juxtaposed in one region of the
- 10 molecule with a double bond providing a center of optical activity, and a hydrophobic tail. Preferably also, at least one hydroxyl and the amino group are either available as such, or freely available for substitution.
- 15 More preferred sphingosine equivalents retain, or will liberate, both hydroxyls, the amino group and the double bond.

Skin-renewal stimulating acids

- 20 In general terms the skin-renewal stimulating acid can be a hydrophilic acid or other acid-equivalent electronegatively hydrophilic organic compound selected from the group consisting of hydroxycarboxylic acids, keto acids, keto esters, hydroxybenzoic acids and related
- 25 compounds. Preferred compounds are relatively lower molecular weight as higher molecular weight compounds tend to be hydrophobic and may have too little activity. Since the smallest molecules such as formic acid, are unduly aggressive and not readily subject to control, a
- 30 preferred molecular weight range is from about 50 to about 250.

Moreover, relevant biological activity appears to require for the simpler, non-receptor binding acids, which lack

35 the hormone-like activity attributable to receptor binding of the retinoids, close proximity between the hydroxyl or keto groups and the carboxyl group. Preferably they should be substituents of one and the same carbon atom.

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5 In one group of preferred embodiments, the skin-cell-renewal stimulating acid is a hydrophilic acid selected from the group consisting of alpha hydroxy carboxylic acids, alpha keto carboxylic acids and hydroxybenzoic acids.

10

Preferably, the acid, or acid equivalent, is selected from the group consisting of glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, mandelic acid, azelaic acid, glyceric acid, tartronic acid, gluconic acid, benzilic acid, pyruvic acid, ethyl pyruvate, 2-hydroxybutyric acid, and mixtures thereof. Although mineral acids in appropriate concentrations, may stimulate skin cell renewal, they are not believed to be susceptible to irritation control by the present invention, nor are highly polar non-hydroxy acids, for example trichloroacetic acid. Ascorbic acid is a special case of a hydroxy acid which has some application in skin-renewal stimulation, but is not generally suitable for incorporation in cosmetic skin-renewal stimulating formulations as it tends to brown in such formulations at active concentrations of about 5 to 10 weight-for-weight. Ascorbic acid, in lower concentrations, has important applicability as an anti-oxidant, in the practice of this invention, as will be described hereinbelow.

30

Preferably, the alpha hydroxy acid used in the inventive compositions is a straight or branched chain aliphatic acid with not more than three substituents in the aliphatic backbone, the substituents being non-basic and being selected from the group consisting of hydroxy, aldehyde, keto, carboxyl, chloro and nitro.

35

In another group of preferred embodiments, the skin-cell-renewal stimulating acid is a hydrophobic acidic retinoid, for example tretinoin, or retinoic acid.

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5 Various skin-renewal stimulating acids may be combined together, and simple tests can be used to evaluate the efficacy and side effects of skin renewal acids, for incorporation into cosmetics suitable for daily application to the skin, hair or nails.

10

The invention is also applicable to, and can use other skin-renewal stimulating acids such as those described in the literature cited above. Preferred are acids with good, cosmetically acceptable characteristics, especially freedom from any unpleasant odor, low or substantially no toxicity, stability for shelf life, freedom from regulatory problems, known and tolerable side effects and a white or colorless, appearance in end product compositions, as well as the ability to be easily formulated in traditional cosmetic compositions. Sphingosine and equivalents preferably also meet these requirements.

Relative proportions of ingredients

25 An effective amount of sphingosine can be found in the range of from about 0.001 to 5% by weight of a topically applied skin treatment composition, preferably, about 0.005 to about 0.2%. Strong activity is shown at concentrations of about 0.01 to 0.1%. Because of the presently high cost of sphingosine, the lowest effective concentrations are preferred.

A suitable concentration of hydrophilic skin-renewal stimulating acid, in cosmetics intended for daily use, is from about 0.1 or 0.15 to about 9 percent by weight of the skin-renewal stimulating-cosmetic composition, preferably about 1 to about 5%. A concentration that stimulates at least a twenty percent increase in skin renewal and induces an immediate irritation level not exceeding 2.0, according to the tests described herein, is preferred. More potent skin peel compositions

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- 5 intended for occasional use, usually with professional supervision, may have a proportion of skin-renewal stimulating acid of up to about 35%.

10 Lower concentrations of a hydrophobic skin-renewal stimulating acid of types such as tretinoin which stimulate cellular receptors, are generally effective. Thus a concentration of such hydrophobic acid of from about 0.005 to about 1.0 percent by weight of the skin-renewal stimulating composition, is preferred with from
15 about 0.01 to 0.1 or 0.5 percent being more preferred.

pH of composition

Skin-renewal stimulating compositions, according to this invention should have substantial acidity and be capable
20 of stimulating a substantially acidic environment when applied to the skin. Consumer use, over-the-counter preparations, intended for daily or twice daily application, should be relatively mild, with a pH of from about 4.5 to about 6.0, or even as mild as 6.2. A
25 preferred pH target is near pH 5, for example from pH 4.8 to 5.2.

Professional-use compositions are more acidic, typically with a pH in the range of from 2.5 to 4.5. Such a
30 professional-use composition, for example a skin peel, is stronger and may have a higher proportion of skin-renewal stimulating acid, for example from 7.5 to 30 weight percent of the composition of a hydrophilic acid, or several percent, up to about five weight percent of the
35 composition.

Preferred cosmetic compositions suitable for frequent topical application to their skin by consumers and formulated according to this invention, with sphingosine,
40 have an acidic pH of from about 2 to about 5.5 and can include, or consist essentially of, cosmetically

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5 compatible, odor-free and preferably colorless or white,
water or alcohol-soluble, skin-cell-renewal stimulating
acids for example, a hydroxybenzoic acid or acids, for
example 2-hydroxybenzoic acid or an alpha hydroxy acid,
for example lactic acid, or mixtures thereof, dissolved
10 in a cosmetically compatible solvent system.

Incorporation of anti-irritants

We have also been able to demonstrate, with comparative
test data, that the efficacy of a skin exfoliant
15 composition, including the inventive skin-renewal
stimulating composition described herein, can be improved
by incorporating significant quantities of one or more
antioxidants or anti-inflammatory agents in the
composition, or both. Common physiologically acceptable
20 and cosmetically compatible antioxidants are vitamins C
and E and the vitamin A precursor, β -carotene. Use of
both vitamin C and vitamin E or β -carotene will provide
both lipid and aqueous phase anti-oxidant functions.

25 One function of antioxidants is anti-irritant, increasing
the effective acid strength, or dose, any particular
individual can tolerate. Other anti-irritants, anti-
inflammatory agents and anti-oxidants can be used, in
suitably effective amounts, which can be from about 0.1
30 to about 20 weight percent of the composition, although
lower concentrations than 20%, for example 10 or 5%
generally more suitable.

Another important function of anti-oxidants is to control
35 long-term free-radical damage, the effects of which can
simulate aging. Free radicals are generated in skin
tissues by skin-renewal stimulating acids and because of
their potent chemical activity free radicals may disrupt
DNA or interfere with protein synthesis. Lacking
40 control, which anti-oxidants can provide, damage
attributable to free radicals can accumulate and may

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- 5 eventually negate or reduce the beneficial effects of skin renewal stimulation.

Some suitable anti-oxidants are selected from the group consisting of vitamin C, β -carotene, vitamin E, or α -
10 tocopherol and its derivatives, (or mixed tocopherols), nor-diguaritic acid (NDGA), oat extract, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ascorbyl palmitate, propyl gallate, rosemary extract, superoxide dismutase, selenium, caffeine, caffeic acid
15 and its derivatives, or mixtures thereof.

BHT, BHA, propyl gallate, NDGA and rosmarinic acid are generally used in rather small proportions, of less than one weight percent, while vitamins C and E, are used in
20 somewhat greater proportions, for example about 1 to 5 weight percent. Some examples of anti-oxidant formulations that can be used with advantage to enhance the skin-renewal stimulating compositions of this invention with approximate percentages by weight of skin-
25 renewal stimulating composition, are:

- 0.3% BHT, 2% vitamin E, 0.1% vitamin C with 0.1% propyl gallate;
- 1% oat extract with 2% superoxide dismutase;
- 5% vitamin C;
- 30 0.3% BHT with 0.1% NDGA; and
- 0.3% BHT with 0.1% rosmarinic acid or rosemary extract.

Some suitable anti-inflammatory agents can be selected
35 from the group consisting of caffeine, theophylline, hydrocortisone, rosemary extract and green tea extract, or mixtures thereof. These agents are preferably used in proportions of about 0.5 to 5.0 weight percent, with the natural extracts being used at the higher end of this
40 range. Some examples of anti-inflammatory formulations that can be used with advantage to enhance the skin-

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- 5 renewal stimulating compositions of this invention, with approximate percentages by weight of skin-renewal stimulating composition, are:
- 5% rosemary or green tea extract;
 - 0.5 to 2% hydrocortisone;
 - 10 1.0% caffeine;
 - 0.2% caffeine with 2.0% theophylline;
 - 1.0% alpha-bisabolol; and
 - 5.0% aloe.
- 15 A further feature of the invention is the use of materials to control short-term, or immediate irritation, when incorporated in the novel skin-renewal stimulating compositions described herein. Preferably, such anti-irritants comprise from about 0.1 to 20 weight percent,
- 20 more preferably to 10 weight percent, of the skin-renewal stimulating composition and are selected from the group consisting of antioxidants and anti-inflammatory agents. For example, from about 1 to about 7 percent of rosemary extract, can be included to reduce immediate, or short-
- 25 term irritation or burning.

Suitable vehicles

- Any cosmetically acceptable vehicles customarily employed for delivering skin-renewal stimulating acids to the
- 30 skin, hair or nails can be employed in the practice of this invention. Suitable vehicles may be aqueous, or hydroalcoholic, or employ oil or other hydrophobics in dispersions to provide common formulations into creams, lotions, tonics and the like. If desired, the vehicle
- 35 can simply be plain water, although small quantities of alcohol or other organic solvent may be needed to dissolve or disperse the small quantities of sphingosine required by the present invention.
- 40 In a preferred embodiment, the active ingredients can be formulated in a cosmetically acceptable hydroalcoholic

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5 vehicle having from about 40 to 75 weight percent of
water, preferably 55 to 65 or about 60%, and from about
25 to 55 weight percent, preferably from about 25 to 35
or about 30 percent of an aliphatic alcohol. While a
number of lower aliphatic alcohols, both monohydric and
10 polyhydric can be used, ethanol and propanol are the most
preferred choices. Many additives and supplemental
materials are known to the art as being useful for
incorporation in such vehicles, for example, glycerine up
to about 5 percent, preferably 1 or 2 percent is useful
15 as a humectant to counteract the drying effect of the
alcohol and to improve the feel of the tonic.
Stabilizers, fragrances and colorants are examples of
other such additives.

20 Other suitable vehicles include a hydrophobic dispersion
of from about 5 to about 60 weight percent of a
hydrophobic fluid dispersed in an aqueous medium, and
water.

25 If necessary, pH adjustment to an acceptable range can be
effected with from 0.1 to 10 weight percent of an
alkaline medium, for example aqueous sodium hydroxide,
arginine or triethanolamine (TEA). Since the pH of the
skin-renewal stimulating compositions of this invention
30 has an important bearing on their efficacy, the presence
of an appropriate buffer may also be desirable. Any such
buffer or buffering system, acting in conjunction with
the alkaline medium, should of course act to provide an
acidic pH within the ranges described above, and
35 preferably to keep the pH at 4.5 or below. The quantity
of buffer will depend upon its strength but will usually
be from about 0.1 to 10 weight percent, preferably about
1 or 2 percent. Some suitable buffers are TRIS
(trimethylolaminomethane) buffers and phosphate buffers.

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5 **SKIN-RENEWAL-STIMULATING ACID: EFFICACY TESTING**

A simple cell renewal assay was used to determine the effectiveness of various skin-renewal stimulant acid compositions in improving skin condition. The ability to promote cell renewal has been found to be an effective marker indicating, or associated with, what are known as anti-aging benefits including, firming of the skin, increasing skin thickness and reducing the appearance of lines and wrinkles.

15 **PROCEDURES****Determination of cell-renewal increase %**

At least five panelists for each test, and preferably twenty, are patched with 5% dansyl chloride, a fluorescent stain, in petrolatum, on four test sites, two on each volar forearm, or elsewhere, as indicated. The subjects are examined on day 1 to ensure the stain has taken. Using three sites on each panelist and leaving the fourth as a control, test samples are applied with Q-tips, to randomized sites. The panelists are examined at intervals, commencing at day 7, using a quartz mineral light to detect the presence of residual stain at the test sites, examination continuing until the stain is removed.

Additionally, on day 1 and at the end of the study, all test sites, including the controls, are gently scrubbed with a detergent solution to remove loosely adhering squames which are then quantified as cell renewal increase %, using known cell counting techniques.

35

Determination of induced irritation

Irritation was evaluated by comparative chromaticity determinations of skin color, by industry standard methods, employing a Minolta Chroma Meter, Minolta Camera Co. Ltd, giving a* readings of skin redness. In general, a* values obtained from the cheeks of volunteers range

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5 from about 6 for very pale whitish skin to about 25 on
very red skin with a sunburned appearance. Preparatory
tests indicated that induction of irritation by
application of methyl nicotinate, or balsam of Peru, to
the skin of volunteers, increased a* readings by about 5-
10 10 units, reflecting severe irritation. For comparative
purposes, an arbitrary scale was devised in which 1.0
irritation unit was equivalent to a difference of 2.5
chromaticity units on the a* scale, as follows:

	<u>Increase in a*</u>	<u>Irritation Index</u>
15	10.0	5.0
	7.5	4.0
	5.0	3.0
	2.5	2.0
	0.0	1.0

20 Additional, subjective perceptions of stinging, burning
and skin redness after application were recorded, and the
data were correlated with the clinical irritation index
tabulated above to provide comparative indications of
25 reported and observed irritation. On this scale of from
0 to 5, 0 indicates no discernible or reported
irritation, and 5 indicates severe irritation.

EXAMPLE 1

Preparation of a skin-renewal-stimulating cream with 30 lactic acid

Phase A:

The following ingredients are combined in the proportions
indicated, being weight-for-weight proportions based on
the final composition, as are all proportions in these
35 examples:

	Water	71.15
	Propylene Glycol	5.00
	Xanthan	0.25
40	Phenoxyethanol	0.30

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- 5 The xanthan gum is added to water while mixing, and heated to
75 °C, when the remaining Phase A ingredients are added.

10

Phase B:

- 15 The following ingredients are heated together, with mixing, until uniform:

	Caprylic or capric triglyceride	4.00
	Stearic Acid	4.50
20	Mineral Oil	6.00
	Dimethicone	1.00
	Cetyl Alcohol	1.50
	Cetearyl Alcohol	
	Ceteareth-20	1.50
25	Glyceryl Stearate	0.75
	PEG-100 Stearate	0.75
	Steareth-2	0.20
	Sphingosine	0.10

- 30 Phase B is added to Phase A and mixed. The mixture is cooled to
40 °C, while mixing. The following alpha hydroxy carboxylic acid
35 is added with mixing and the mixture is cooled to 25 °C:

Phase C:

40	Lactic acid	3.00
----	-------------	------

The pH is adjusted, if necessary to 3.5 to 5.0.

45

EXAMPLE 2

- 50 Preparation of a skin-renewal-stimulating lotion with lactic acid

The procedure of Example 1 was repeated using the following

- 55 ingredients in the weight-for-weight proportions indicated:

60

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5 **PHASE A:**

	Water	82.65
	Propylene Glycol	5.00
	Xanthan	0.05
10	Phenoxyethanol	0.30

15 **PHASE B:**

	Stearic Acid	1.20
	Mineral Oil	2.00
	Lanolin Oil	2.00
	Dimethicone	0.50
20	Cetyl Alcohol	1.50
	Cetearyl Alcohol with	
	Ceteareth-20	0.50
	Glyceryl Stearate	0.50
	PEG-100 Stearate	0.50
25	Steareth-2	0.20
	Sphingosine	0.10

30 **PHASE C:**

30	Lactic Acid	3.00
----	-------------	------

35 **EXAMPLE 3**Preparation of a skin-renewal-stimulating toner with lactic acid

40 The following ingredients are mixed together until uniform:

	Lactic Acid	1.00
	Ethanol SDA 40	50.00
45	Benzyl Alcohol	0.10
	Sphingosine	0.05
	PPG-5-Ceteth 20	1.00
	PPG-3 Myristyl Ether	0.50
50	Water	47.35

50 The manufacturing approach used in these examples is generally applicable to the formulation of a wide range of cosmetic materials having skin-renewal stimulating properties with long-term control of irritation,

55 according to this invention. In general terms, an

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5 appropriate alpha hydroxy or other acid is dissolved in
suitable, cosmetically acceptable or compatible solvents
and the resultant solution, or solutions, is admixed with
conventional cosmetic ingredients, including
moisturizers, humectants, stabilizers, fragrances,
10 colorants and the like, as desired by the formulator or
customer. Optional ingredients of the invention, such as
buffers and anti-irritants, including anti-inflammatories
and anti-oxidants, can also be incorporated, as
appropriate.

15

Skin-renewal Stimulation Efficacy of Various Skin Lipids
Four skin lipid materials were examined individually,
without other agents present, to determine their
abilities, if any, to stimulate skin cell renewal. The
20 lipids comprised bovine brain extracts of research grade
material with greater than 90% purity of cerebrosides,
ceramides and sphingosine, at the concentrations shown,
supplied by Sigma Chemical Co., St. Louis, Missouri.
The phospholipid employed in these examples was research
25 grade, purified soy lecithin, also from Sigma Chemical
Co.

These four materials constituted the examined skin
lipids. The examined skin lipids were agitated and
30 dissolved or dispersed in a 1:1 water/ethanol SD 40
solvent vehicle. Where appropriate, the pH was adjusted
with 99% TEA (triethanolamine). These solutions or

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5 dispersions of skin lipids to be examined were
incorporated into cosmetic test samples to provide the
desired concentrations.

Test samples, in the following tests, comprise aliquots of
10 skin-renewal stimulating cream compositions (or controls)
based on that set forth in Example 1 with variations of
proportions, conditions and ingredients, as shown in the test
results tabulated below. The data set forth in Table 1 were
obtained using the above-described skin lipid materials alone:

15

TABLE 1

		<u>Concentration</u>	<u>%</u> <u>in Cell</u>
20	<u>Increase</u> <u>Material</u> <u>Renewal</u> phospholipids	0.01%	+0.6%
		1.00%	+1.4%
		10.00%	+7.3%
25	cerebrosides	0.1 %	+4.5%
		1.00%	+11.2%
	ceramides	0.1 %	+3.7%
30		1.00%	+6.6%
	sphingosine	0.1 %	+2.2%
		0.01%	+4.9%
		1.00%	+7.9%
35	vehicle (control)	100.00%	+4.5%

Referring to Table 1, it can be seen that although the
40 examined skin lipid constituents provide a small stimulation
or increase of cell renewal the degree is minimal. Looking to
the foot of the table, the control vehicle alone provides a
base line stimulation of 4.5%. Accordingly, any stimulation

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5 below 4.5% is of not of interest for a commercial product
having useful activity. The phospholipid, at a concentration
of 10%, ceramides at a concentration of 1.0% and sphingosine
at a concentration of 1.0% provide an increase of cell renewal
in a range of from 6% to 8% slightly above the control value,
10 but not enough to be of significant commercial interest.
Cerebrosides at a concentration of 1.0% show a somewhat
greater stimulation at 11.2% increase in cell renewal. This
figure is still quite modest when compared with an increase of
20-30% which is obtainable with a number of simple,
15 inexpensive acids, including alpha hydroxy acids.
Accordingly, these four classes of skin lipids are of little
interest for stimulating cell renewal although cerebrosides
show somewhat more activity than the other materials. None
looks suitable as an alternative to a retinoic or alpha
20 hydroxy skin-renewal stimulant. Note, this was a clinical
study performed on human volunteers and is believed to be more
indicative of the actual performance of topically applied
cosmetic ingredients than are in vitro or animal studies.

25 Control of Immediate Irritation by the Examined Skin Lipids

The ability of the examined skin lipids to control "immediate"
irritation was determined by comparative chromaticity
measurements of the skin of volunteers after treatment with
balsam of Peru at time zero and after 30 minutes. "Immediate"
30 is used in the sense of an irritation reaction inducing a
physiological response that commences immediately upon
application of the test sample, although it may take some

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5 minutes to peak and become perceptible. The effect is a primary irritation effect that can be contrasted with secondary, long-term irritation that may take weeks to develop. In Table 2, the results from clinical experiments employing 1% concentrations of a phospholipid, cerebroside, ceramides, and sphingosine show the respective abilities of these substances to control immediate irritation, as compared with water and a known anti-irritant, 5% rosemary extract.

15

TABLE 2

20	<u>Skin Treatment</u> <u>min.</u>	<u>a* value</u> <u>time=0 min.</u>	<u>a* value</u> <u>time=30</u>
	no treatment	6.2	6.1
	8% balsam of Peru	6.1	15.2
	water only	6.0	13.9
25	positive control (5% Kola)	6.1	7.7
	1% phospholipids	6.2	14.4
	1% sphingosine	6.1	13.9
	1% ceramides	6.0	14.2
30	1% cerebroside	6.2	14.9

Referring to Table 2, at time zero before the irritation due to the balsam of Peru had time to develop, all the test samples had very similar a* readings on the Minolta Chromaticity Meter, indicative of normal skin color. The results at thirty minutes show reddening to a reading of 15.2 for balsam of Peru alone and that water alone reduces this reddening slightly (to 13.9). The positive control, a 5% kola anti-irritant solution exhibited a marked suppression of the irritant effect of balsam of Peru, reducing the thirty-minute reddening to an a* reading of 7.7. None of the examined skin

- 5 lipids was any better than water in reducing 30-minute reddening.

Clearly, from these data, none of the examined skin lipids is suitable for use as a topical anti-irritant to control
10 immediate or short-term irritation, or more specifically as a short-term suppressant of balsam-of-Peru-induced irritation. To explore the possibly more subtle properties that our theory suggested sphingosine might have, more difficult and elaborate longer term studies were conducted, the results of which are
15 reported in Table 3. Irritation is reported in terms of the index described above, as a differential chromaticity measurement, or Δa^* . A base composition comprising 1% lactic acid and 2% 2-hydroxybenzoic acid in a hydroalcoholic toner solution, at a pH of about 3 was used as a skin-renewal
20 stimulating acid composition. A suitable cosmetically acceptable hydroalcoholic vehicle having from about 40 to 75 weight percent of water, preferably 55 to 65 or about 60%, and from about 25 to 55 weight percent, preferably from about 25 to 35 or about 30 percent of an aliphatic alcohol, preferably
25 propanol, or alternatively ethanol, is used. Additives and supplemental materials known to the art as being useful for incorporation in such vehicles, for example, glycerine up to about 5 percent, preferably 1 or 2 percent is useful as a humectant to counteract the drying effect of the alcohol and
30 to improve the feel of the tonic, stabilizers, fragrances and colorants, can also be used.

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5 If necessary, pH adjustment to an acceptable range can be
 effected with from 0.1 to 10 weight percent of an alkaline
 medium, for example aqueous sodium hydroxide, arginine or
 triethanolamine (TEA). A composition of 2-hydroxybenzoic acid
 and lactic acid is effective in stimulating skin cell renewal
 10 while exhibiting low levels of immediate irritation.

Panelists in the following tests, applied test samples to test
 sites, as described above. At least five panelists were used
 for each result. For long-term irritation and skin-renewal
 15 stimulation determinations, test samples were applied on a
 twice daily basis, morning and night. The test samples
 comprised aliquots of skin-conditioning cream compositions
 equivalent to the composition set forth in Example 1
 hereinabove, with the addition of the respective test
 20 ingredients, as appropriate. Tretinoin was used in a
 commercially available cosmetic formulation in a concentration
 of about 0.05%.

TABLE 3

25	Cell		Irritation Induced	
	<u>Renewal</u> <u>Weeks Use</u>	<u>Composition</u> <u>% Incr.</u>	<u>Immediate</u>	<u>After 4</u>
30	Base composition (alone)		2.6	2.2
	22			
	Base with the indicated additional ingredient:			
	0.1% phospholipids	2.5	2.0	20
35	1.0% phospholipids	3.0	2.2	25
	0.1% cerebrosides	2.4	2.1	21
	1.0% cerebrosides	2.3	2.1	19
40	0.1% ceramides	2.4	2.3	18
	1.0% ceramides	2.3	2.2	22
	0.1% sphingosine	2.3	1.5	23

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5	1.0% sphingosine	2.4	1.8	18
	0.01% sphingosine	2.3	1.6	21
	positive control			
	5% kola nut extract		1.4	1.7
10		20		
	tretinoin* alone	1.7	3.1	33
	tretinoin* with			
	0.1% sphingosine	1.8	2.2	34
15				

Table 3 shows the effect of the four classes of examined skin lipids, at different concentrations, upon irritation levels induced by the base composition of skin-renewal stimulating hydroxy acids, after four weeks of continuous daily use. Their efficacy as skin-renewal stimulants is also reported. To understand whether the test material exerts any long-term control of irritation, the four week reading has to be compared with the immediate reading. Any significant reduction, at four weeks, is suggestive that the test material is effective in controlling long-term irritation. For any apparent activity to be significant, the degree of suppression of irritation should reduce the irritation index below the figure for the base alone. The first line of data in Table 3 shows that the unsupplemented base composition exhibits a decline, from an irritation index value of 2.6, induced immediately (30 minutes) after application of the base hydroxy acid skin-renewal promotion composition, to 2.2 after four weeks of use.

Seen in this light, only sphingosine, at all concentrations, shows a significant reduction of long-term irritation with a decline, for the 0.1% sample of more than 30% of the scale

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5 value, from 2.3 to 1.5. The other examined skin lipids show little, if any reduction. The results for a 1% concentration of phospholipids are anomalous in that the immediate reported effect of the phospholipid in this test was to increase the irritation level. The resultant decline at four weeks was to
10 a figure substantially the same as that for the base used alone. Clearly, the tested phospholipid is of no interest in controlling long-term irritation induced by the base hydroxy acid composition.

15 When used with the 2-hydroxybenzoic acid-lactic acid skin-renewal stimulant base described above, sphingosine exerted a pronounced long-term irritation-controlling effect which, surprisingly, was not exhibited by the other classes of examined biologically active skin lipids namely the
20 phospholipids, cerebrosides and ceramides. Reference to the cell renewal percentage increases reported for various combinations of the cell-renewal stimulant acid, or acids, and examined skin lipids shows that, in general, the presence of the examined skin lipid materials had little depressant effect
25 upon the cell-renewal stimulatory activity of the base composition. A concentration of 0.1% sphingosine was particularly interesting, showing the lowest irritation level at four weeks of any material tested. That concentration of sphingosine also exhibited the best cell-renewal percentage
30 increase of the sphingosine samples and at 23% this was one of the higher results for samples employing a 2-hydroxybenzoic acid-lactic acid base.

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5 The positive control, a 5% kola anti-irritant solution had an immediate effect of substantially suppressing irritation but, in spite of the continued presence of kola in the test composition, by four weeks the irritation level had risen substantially, from 1.4 to 1.7, indicating a long-term
10 irritation phenomenon not subject to control by topically applied kola.

Kola nut or rosemary extract and other anti-irritants are of course optional ingredients for inclusion in the novel
15 compositions of this invention. Combined with sphingosine, such anti-irritants can be expected to produce good control of both immediate irritation and long-term irritation, and the four-week values may even be improved over those shown in Table 3, by such a combination. Because sphingosine is a
20 subtle biochemical agent capable of mediating cellular activity, we believe that the benefits brought to skin-renewal stimulating compositions by the presence of sphingosine, according to the teachings of the present invention, may be more pronounced with periods of use longer than the four weeks
25 that was practical for the above tests. Normal use is for eight to twelve weeks, which may then be followed by maintenance usage for indefinite periods. Accumulative small benefits become more significant over extended periods of use, especially with large populations of users. Also, sphingosine
30 may bring subtle advantages of skin conditioning that are only manifested with extended use.

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5 A concentration of 0.1% sphingosine has a dramatic effect when
used in combination with tretinoin, as revealed by this test
regimen. Referring to the next to last line of Table 3, the
long-term irritation capability of tretinoin is clearly shown
as rising to 3.1 after four weeks from a modest initial value
10 of 1.7 when tretinoin is used alone. When 0.1% sphingosine is
added to tretinoin (last line of Table 3), tretinoin's severe
four-week irritation is substantially reduced from 3.1 to 2.2.
The high skin cell-renewal stimulant activity of tretinoin was
not diminished.

15

In summary, the comparative data of Table 3 shows that
sphingosine alone of the examined skin lipids displays a
distinct ability to control four-week irritation induced by
multiple classes of skin-renewal stimulant acids without
20 significantly diminishing their activity.

The effect of sphingosine on individual alpha hydroxy
carboxylic acids was determined by conducting cell renewal and
four week irritation tests as described above. The following
25 results were obtained.

TABLE 4

Efficacy		% Increase		Irritation	
30	<u>Safety</u> <u>Composition</u> <u>Factor</u>	<u>in Cell Renewal</u>		<u>Induced</u>	
35	2% lactic acid pH 3	22	2.6	8.46	
	+ 0.01% sphingosine	23	1.9	12.10	
	+ 0.10% sphingosine	26	1.6	16.25	
	2% lactic acid pH 6	16	1.9	8.42	
	+ 0.10% sphingosine	24	1.4	17.14	

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5	5% lactic acid pH 6 + 0.10% sphingosine	29	3.5	8.29
		30	2.2	13.63
10	1% 2-hydroxybenzoic acid pH 3 + 0.10% sphingosine	22	2.5	8.80
		24	1.9	12.63
10	1% 2-hydroxybenzoic acid pH 6 + 0.10% sphingosine	17	2.2	7.7
		26	2.0	13.0

15 The efficacy safety factor used in this table weights the cell-renewal stimulating activity of the hydroxy acid against the irritation induced by dividing the cell renewal % increase by the irritation level. Referring to the data in this table, it can be seen that sphingosine has a modest ability to

20 stimulate the cell renewal increasing capability of simple alpha hydroxy acids, such as lactic acid and 2-hydroxybenzoic acid. The preferred concentration of 0.1% sphingosine was effective in raising the cell renewal percentage increase by three points for a 2% lactic acid solution at the more

25 strongly irritating pH of 3, and by eight points at pH 6 with comparable numbers being shown for 2-hydroxybenzoic acid. There is little improvement of cell renewal stimulation when a higher concentration of about 5% of lactic acid is used. Here, the cell renewal efficiency is probably close to a

30 maximum, at 29%, and is hard to improve. The overall impact of sphingosine on the suitability of hydroxy acids such as lactic acid and 2-hydroxybenzoic acid for skin-renewal stimulation with controlled long-term irritation, is clearly demonstrated by comparing the higher values of the efficacy

35 safety factor obtained when sphingosine is present with the lower values obtained when it is not.

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5 In general, cosmetic formulations with a pH of the order of 6 are suitable for over-the-counter consumer sales for daily use, while those with a lower pH of 3 are more suitable for use under professional supervision by physicians or licensed beauticians.

10

The potential wider applicability of the invention to controlling, or compensating for, undesired side effects of cell-proliferation stimulating agents, at large, is suggested by the following data in Test 5. To obtain the reported results, subjects on aggressive alpha hydroxy acid therapy for clinical skin disorders were evaluated for sphingosine content in their skin. The surface of the skin of test subjects was swabbed several times with methanol to extract methanol-soluble skin-lipid components. The extracts were pooled, dried and resuspended in 100 μ l. 1:1 chloroform/methanol and examined by high performance thin-layer chromatography. Calibration against standards for sphingosine, ceramides and cerebrosides, using densitometry, enabled changes in sphingosine to be quantified. Determinations were made on subjects before treatment, after four weeks and after eight weeks. The results are shown in Table 5.

TABLE 5

30	<u>Skin lipid component</u>	<u>% change after</u>	
		<u>four weeks</u>	<u>eight weeks</u>
	ceramides	n.s.	n.s.
	cerebrosides	n.s.	- 8%
	sphingosine	- 11%	- 37%

35 "n.s." is "not significant".

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- 5 These findings show a clear and selective decline in sphingosine levels accompanying alpha hydroxy acid treatment. This decline is not shared by the other skin lipid components tested, there being no apparent decline of ceramides and only a minor decline of cerebrosides.
- 10 This data leads to the conclusion that a decline in sphingosine may be an important side-effect of the altered skin metabolism wrought by cell-renewal stimulating acids such as alpha hydroxy acids.
- 15 While this invention is not limited by any particular theory, we have developed a theory, not taught by any prior art known to us, that relates our discoveries regarding sphingosine to concepts of cell proliferation and differentiation. In accordance with our theory, it
- 20 appears that a high degree of cell renewal stimulation may reduce or hinder differentiation. Thus the peeling brought about as an early effect of strong skin acid compositions is a desquamation of immature cells resulting from over-stimulation of cell renewal. In
- 25 time, the stimulus is less and more mature cells are generated.

Cerebrosides, ceramides and sphingosine are known to be substantially interconvertible in skin tissues.

- 30 Cerebrosides lose a sugar to become ceramides. Cleavage of a fatty acyl chain from ceramides yields sphingosine. Sphingosine is synthesized in basal keratinocytes in

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5 inner layers of the skin. It is also known that
maturation of the epidermis, proceeding outwardly to the
skin surface, is accompanied by a decrease in content of
cerebrosides while ceramides increase. Ceramides are a
potential exogenous source of sphingosine, by de-
10 acylation, as described above.

With this background, we have speculated that if cells
are stimulated to grow faster than normal, they have too
little time to produce adequate sphingosine. It has
15 occurred to us that ceramide breakdown rates, as the
cells mature into stratum corneal cells, may be
inadequate. Or synthesis of sphingosine in basal
keratinocytes may be inadequate. This speculation is
verified by, and represents an interpretation of, the
20 findings reported in Table 5. Noting the importance of
sphingosine-based ceramides to the barrier function of
epithelial tissues, the data of Tables 1-4, when seen in
the light of this hypothesis, suggest this invention may
have a wide applicability to controlling side effects of
25 cell proliferation stimulants by applying or
administering sphingosine along with such stimulants.

Besides the skin-renewal stimulating acids described
herein, other agents such as drugs and hormones are
30 capable of stimulating epithelial cell proliferation, for
example retinoid drugs, vitamin D₃ also known as
cholecalciferol, epithelially active growth hormones, for

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5 example somatotropin also known as human growth hormone,
epidermal growth factor and various glandular extracts.
Pursuant to the foregoing insights, the present invention
includes uses of sphingosine that are effective to
control side effects of such other agents.

10

Thus, in this aspect, the invention provides a cell-
renewal stimulating composition for topical application
to epithelial tissue comprising sufficient of an active,
cell-renewal stimulating agent to stimulate increased
15 cell proliferation, which agent can induce deferred
hyperproliferative allergenicity and is formulated
together with a proportion of sphingosine material
sufficient to compensate for sphingosine deficiencies
attributable to cellular immaturity.

20

Preferably, the cell-renewal stimulating agent is
selected from the group consisting of hydrophilic, skin-
cell-renewal stimulating acids, hydrophobic skin-cell-
renewal stimulating hydrophobic acids, cell-proliferation
25 stimulating hormones and cell-proliferation stimulating
drugs. However less specifically active products, for
example moisturizing cosmetics, which though not
incorporating a skin-cell-renewal stimulating acid,
nevertheless display a delayed irritation attributable to
30 skin cell hyperproliferation, can be improved by
incorporating a sphingosine material, in the manner

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5 described herein, to control delayed or long term
irritation.

Preferably, the inventive cell-renewal stimulating
composition is for topical application to normal skin on
10 a frequent basis, and has an acidic pH, wherein the cell-
renewal stimulant agent is a skin-cell renewal stimulant
acid or acids present at a sufficient concentration to
improve the appearance of the skin, the sphingosine being
present at a sufficient concentration to control long-
15 term irritation.

Application Rates and Frequencies

Typical application rates of the inventive skin-renewal
stimulating compositions described herein can range from
20 about 0.01 to 0.5 mg of active acid ingredients per square
centimeter of skin, where the acid is a low-molecular
weight hydrophilic acid, such as an alpha hydroxy
carboxylic acid, with a range of from 0.05 to 0.2 mg/cm²
being preferred. Cosmetic creams are generally applied
25 at a rate of about 2-3 mg/cm². With an active ingredient
proportion of about 0.15 to about 30 weight percent, this
gives a possible rate of application of active
ingredients of from about 0.003 mg/cm² to 0.9 mg/cm². A
preferred range is from about 0.01 to 0.5 mg/cm², with a
30 range of from 0.05 to 0.2 mg/cm² active ingredient per
unit skin area being more preferred. Using a preferred
proportion of about 3% active acidic ingredients, in

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5 total, gives a preferred application rate of 0.06 to 0.09
mg/cm².

Hydrophobic skin-renewal stimulating acids, such as
retinoic acids are usually used in substantially lower
10 concentrations, for example from 20 to 200 times less
concentrated.

This dosage is applied to whatever skin area requires
treatment, preferably twice a day. More frequent
15 applications of three or four times a day are likely to
be wasteful of product without providing additional
benefits, whereas less frequent applications, notably
once a day, result in reduced efficacy. Additional
applications may occasionally be made after washing,
20 bathing or swimming, up to a maximum of about six times a
day.

The inventive use of sphingosine in skin-renewal
stimulant compositions is of particular value in
25 controlling long-term irritation in daily or repeated use
cosmetic formulations. The formulations described herein
are generally lower strength non-prescription or consumer
preparations although advantages may also be obtained
using sphingosine in higher-strength professional
30 preparations intended for use under the supervision of
dermatological professionals. Such higher strength
preparations will be more acidic, with a pH below about

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5 4.0, for example in the range of from 2.0 to 3.5. They will also have a higher concentration of acidic ingredient or ingredients, with sphingosine incorporated in a proportionately higher concentration. Such higher concentration can be in the range of about 10 to 30

10 weight percent of the composition of hydrophobic skin-renewal stimulant acid. For a hydrophobic, cell-membrane receptor-active, skin-renewal stimulant, such as a retinoic acid, a higher concentration of about 0.1 to 1.0 weight percent can be used. Such high-strength

15 compositions generally are skin peels, acting to cause skin to peel after only one or two treatments. High strength compositions are generally not suitable for frequent, repeated application.

20 Long-term irritation, control of which is a benefit provided by sphingosine, is compounded by frequent applications of a skin-renewal stimulant acid. Many daily use cosmetic preparations on the market now include a skin-renewal stimulating acid that may produce such

25 long-term irritation. Indeed, conventional moisturizer formulations, lacking skin-renewal stimulating acids, can also induce hyperproliferation of skin cells. Inclusion of sphingosine as well as a short-term or immediate anti-irritant and an anti-oxidant, in accordance with the

30 teachings of the invention herein, can alleviate these problems.

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5 The consumer preparation is used on any desired skin area, including the face, while the professional preparation can be applied to spot defects. The consumer composition can be helpful in alleviating problems of wrinkles, sun damage and cracking with some effect on age spots, while the professional composition can be more effective on age spots, keratoses and other more serious skin problems.

One preferred regimen comprises a regular program of twice daily treatments for an indefinite period employing a consumer-use formulation preferably having the more preferred ingredients and proportions of the invention, as set forth above. Such preferred compositions desirably have a proportion of active hydrophilic acid ingredients of about 2-7% and a pH in the range of about 4.5 to 6.0, preferably, close to 5. Such a continual regimen is preferably accompanied by dermatological clinic visits to monitor progress. While a high initial dose to obtain prompt improvement could be used, such may elicit a high initial irritation rate. These above-described dosages are generally appropriate for the application of a skin-renewal stimulating cream to most exposed or exposable skin surfaces, but such would generally not be appropriate for application to the scalp.

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- 5 An alternative regimen comprises a twice daily treatment for about 8 to 12 weeks followed by maintenance applications of the the inventive composition on a daily basis, or about three times per week.

While an illustrative embodiment of the invention has been described above, various modifications will be apparent to those of ordinary skill in the art. Such modifications are within the spirit and scope of the invention, which is limited and defined only by the appended claims.

INDUSTRIAL APPLICABILITY

The inventive compositions disclosed herein are applicable in the cosmetics industry and the pharmaceutical industry.

Claims

5 Claim 1. A skin-renewal-stimulating, cosmetic composition for frequent topical application to normal skin, said composition having an acidic pH in a range of from about pH 4.5 to about 6.2 and comprising;

10 a) a cosmetically acceptable, skin-cell-renewal stimulating acid or acids present in said composition at a sufficient concentration of from about 0.1 to about 15 percent by weight to improve the appearance of the skin, said skin-cell-renewal stimulating acid being selected
15 from the group consisting of alpha hydroxycarboxylic acids, alpha keto carboxylic acids and hydroxybenzoic acids;

said composition being characterized by further comprising

20 b) a proportion of from about 0.001 to about 5 percent by weight of said composition of a sphingosine material to control long-term irritation induced by said skin-cell-renewal stimulating acid, said sphingosine material
25 being selected from the group consisting of sphingosine, phytosphinganine, and dihydrosphingosine, analogs, homologs, enantiomers and derivatives thereof and mixtures of the foregoing.

- 5 Claim 2. A cosmetic composition according to claim 1
characterized in that said skin renewal acid, or acid
equivalent, is selected from the group consisting of
glycolic acid, lactic acid, malic acid, tartaric acid,
citric acid, ascorbic acid, mandelic acid, azelaic acid,
10 glyceric acid, tartronic acid, gluconic acid, benzylic
acid, pyruvic acid, ethyl pyruvate, 2-hydroxybutyric
acid, and mixtures thereof.
- 5 Claim 3. A cosmetic composition according to claim 1 or
2 comprising from about 0.1 to 20 weight percent of an
anti-irritant selected from the group consisting of
antioxidants and anti-inflammatory agents.
- 5 Claim 4. A skin-renewal stimulating composition
according to claim 1, 2 or 3 characterized by being
formulated as a tonic for application to skin, nails or
hair, with a cosmetically acceptable solvent system
selected from the group consisting of a hydroalcoholic
10 vehicle having from about 40 to 75 weight percent of
water and from about 25 to 55 weight percent of an
aliphatic alcohol, a hydrophobic dispersion of from about
5 to about 60 weight percent of a hydrophobic fluid
dispersed in an aqueous medium, and water.
- 5 Claim 5. A cosmetic composition according to claim 1
characterized in that said sphingosine material comprises
a sphingosine substance having a molecular structure with

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5 an electropositive amino nitrogen atom proximate to at
least one electronegative oxygen atom, said molecular
structure being juxtaposed with a double bond to provide
a center of optical activity, and a hydrophobic tail with
said amino group and a proximate electronegative
10 nitrogent atom being available for substitution.

5 Claim 6. A cosmetic composition according to claim 1
characterized in that said sphingosine material is
sphingosine.

5 Claim 7. A cosmetic composition according to claim 1
characterized in that said long-term irritation
controlled by said sphingosine material is irritation
induced by said acid after at least four weeks topical
application of said acid.

5 Claim 8. A skin-renewal-stimulating, professional
dermatological skin peel composition having an acidic pH
in a range of from about pH 2.5 to about 4.5 and
comprising;

a) a cosmetically acceptable, skin-cell-renewal
10 stimulating acid or acids present in said
composition at a sufficient concentration of
from about 7.5 to about 35 percent by weight to
improve the appearance of the skin, said skin-
cell-renewal stimulating acid being selected
15 from the group consisting of alpha hydroxy

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5 carboxylic acids, alpha keto carboxylic acids
 and hydroxybenzoic acids;

said composition being **characterized by further**
comprising:

10 b) a proportion of from about 0.001 to about 5
 percent by weight of said composition of a
 sphingosine material to control long-term
 irritation induced by said skin-cell-renewal
 stimulating acid, said sphingosine material
15 being selected from the group consisting of
 sphingosine, phytosphinganine, and
 dihydrosphingosine, analogs, homologs,
 enantiomers and derivatives thereof and
 mixtures of the foregoing.

5 Claim 9. A cosmetic composition according to claim 8
 characterized in that said sphingosine material is
 sphingosine and said long-term irritation controlled by
 said sphingosine material is irritation induced by said
 acid after at least four weeks topical application of
10 said acid.

5 Claim 10. A cosmetic composition according to claim 8 or
 9 **characterized in that** said skin renewal acid, or acid
 equivalent, is selected from the group consisting of
 glycolic acid, lactic acid, malic acid, tartaric acid,
 citric acid, ascorbic acid, mandelic acid, azelaic acid,
10 glyceric acid, tartronic acid, gluconic acid, benzylic

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- 5 acid, pyruvic acid, ethyl pyruvate, 2-hydroxybutyric
acid, and mixtures thereof.
- 5 Claim 11. A cosmetic composition according to claim 8, 9
or 10 **characterized by** comprising from about 0.1 to 20
weight percent of an anti-irritant selected from the
group consisting of antioxidants and anti-inflammatory
agents.
- 5 Claim 12. A cosmetic composition according to claim 11
characterized in that said anti-irritant is selected from
the group consisting of vitamin C, vitamin E or α -
tocopherol, superoxide dismutase, nor-diguaritic acid,
butylated hydroxyanisole, butylated hydroxytoluene, beta-
10 carotene, aloe and allantoin and derivatives of said
foregoing anti-irritants.
- 5 Claim 13. A cosmetic composition according to claim 11
characterized by comprising from about 0.1 to 10 weight
percent each of both an antioxidant and an anti-
inflammatory agent.
- 5 Claim 14. A skin-renewal-stimulating, cosmetic
composition for repeated topical application to normal
skin, said composition having an acidic pH of from 2.5 to
6.2 and comprising:
- 10 a) from about 0.005 to about 5.0 percent of a
cosmetically acceptable, skin-cell-renewal

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5 stimulating retinoic acid or acids to improve
the appearance of the skin;

said composition being **characterized** by further
comprising:

b) and a proportion of from about 0.001 to about 5
10 percent by weight of said composition of a
sphingosine material to control long-term
irritation induced by said skin-cell-renewal
stimulating acid, said sphingosine material
being selected from the group consisting of
15 sphingosine, phytosphinganine, and
dihydrosphingosine, analogs, homologs,
enantiomers and derivatives thereof and
mixtures of the foregoing.

5 Claim 15. A cosmetic composition for frequent topical
application to normal skin according to claim 14
characterized by comprising from about 0.01 to about 1.0
percent of a retinoic acid and from about 0.005 to about
0.2 percent sphingosine, and further **characterized in**
10 **that** said long-term irritation controlled by said
sphingosine material is irritation induced by said acid
after at least four weeks topical application of said
acid.

5 Claim 16. A cosmetic composition according to claim 14 or
15 **characterized by** comprising from about 0.1 to 20
weight percent of an anti-irritant selected from the

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- 5 group consisting of antioxidants, anti-inflammatory agents and mixtures thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/08388

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A61K 7/00, 7/48

US CL : 424/401; 514/844, 847

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/401; 514/844, 847

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 5,190,876 (MERRILL, JR. ET AL) 02 March 1993, see columns 1 and 6.	1, 2, 14, 15
Y	US, A, 5,149,860 (ZYSMAN ET AL.) 22 September 1992, see columns 1 and 6.	1-3, 5-10, 14, 15
Y	US, A, 5,002,760 (KATZEV) 26 March 1991, see columns 1-4.	1-3, 5-10, 14, 15
Y	US, A, 4,952,683 (TSCHANNEN ET AL.) 28 August 1990, see column 3.	1-3, 5-10, 14, 15
Y	US, A, 4,105,783 (YU ET AL.) 08 August 1978, see columns 1-8.	1-3, 5-10, 14, 15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be part of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z*	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

14 SEPTEMBER 1994

Date of mailing of the international search report

14 NOV 1994

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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/08388

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 4, 11-13
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

3/29/99

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.